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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/776,786	05/01/97	BARKATS	M	ST94065-US

HM12/0405

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	13

DATE MAILED: 04/05/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/776,786	Applicant(s) Barkats et al.
	Examiner Scott D. Priebe, Ph.D.	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Feb 26, 1999*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *27-38, 40, 41, and 44-55* is/are pending in the application.

Of the above, claim(s) *32 and 33* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *27-31, 34-38, 40, 41, and 44-55* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Prosecution Application

The request filed on Feb. 26, 1999 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/776,786 is acceptable and a CPA has been established. An action on the CPA follows. Since no response was filed to the final Office action of Aug. 31, 1998, the action has been essentially repeated below except for the responses to Paper No. 10 filed Jul. 23, 1998.

Election/Restriction

Applicant's election with traverse of Group I, claims 27-31 and 34-55 in Paper No. 9 filed July 23, 1998 has been acknowledged. The traversal was on the ground(s) that the two groups share the same special technical feature of the adenoviral vector and that no search burden would be imposed. This is not found persuasive because the special technical feature of the two groups is the combination of vector and transgene, not merely the vector, which was known in the prior art and therefore not a special technical feature. Whether or not search of both groups would impose a search burden is irrelevant, as search burden is not a criterion under which restriction is required according to PCT rules.

The requirement is still deemed proper and therefore remains FINAL.

Claims 32 and 33 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 9.

This application contains claims 32 and 33 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 101

Claims 48-55 remain rejected under 35 U.S.C. 101 for the reasons of record set forth in the Office action of Jan. 21, 1998 because the claimed invention is directed to non-statutory subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-31, 34-38, 40, 41 and 44-55 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of Jan. 21, 1998 as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 44-47 and 51-55 remain rejected under 35 U.S.C. 112, first paragraph, for those reasons of record set forth in the Office action of Jan. 21, 1998, repeated below, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to pharmaceutical compositions and implants comprising adenoviral vectors comprising DNA encoding a glutathione peroxidase. The specification teaches that the claimed products are to be used for either *ex vivo* gene therapy, e.g. implants, or *in vivo* gene therapy, which would encompass the pharmaceutical compositions (specification, paras. bridging pages 2-3 and 11-12; page 3, lines 15-19; and page 16, lines 18-25). Since the specification must enable the use of these products and the only utility taught is gene therapy, gene therapy using these products must be fully enabled by the specification, unless the product has another utility readily apparent to one skilled in the art. While one may argue that the adenovirus and transfected cells can be used simply to produce glutathione peroxidase *in vitro,* there is no readily apparent non-therapeutic utility for either the pharmaceutical compositions or the implants.

The specification teaches that the invention can be used to treat neurodegenerative diseases, which include Parkinson's disease, Alzheimer's disease, Huntington's disease and ALS,

and other diseases or conditions such as trisomy 21, atherosclerosis, cardiovascular disease, cirrhosis or the liver, diabetes, the formation of cataracts, cranial traumas, neoplasms, and the aging process. No nexus is provided in the specification between either the causes or symptoms of any of these diseases and any preventative, palliative or curative effects that may result either from the intracellular production or secretion of glutathione peroxidase as the result of either *in vivo* or *ex vivo* gene therapy. Rather, the specification that free radicals "may be responsible for" a variety of diseases or conditions that the prior art teaches were due to other causes. The specification provides little detail on how the invention should be used for its stated purpose, to treat neurodegenerative disease and other diseases. The specification directs the skilled artisan to determine the effective dose empirically, and provides a fairly complete list of all commonly used administration routes from which to choose, with no discussion as to which routes would be suitable or effective for the treatment of specific diseases or conditions. There is no specific guidance provided for treatment of any specific disease or condition, and the etiology and effective treatment of each would be expected to be quite different each one from the others. The specification provides no working examples of the claimed method or the disclosed use of the claimed cells or implant. With respect to the disclosed use for the claimed products and the claimed method, the specification does not teach what level of glutathione peroxidase would constitute an effective level to effect the desired treatment or how long the level would need to be maintained. The specification also fails to disclose any therapeutic endpoint or any methodology for determining whether a particular treatment protocol was successful.

The prior art is silent on the treatment of any disease or condition with glutathione peroxidase or by gene therapy with a vector expressing glutathione peroxidase. With respect to diseases of the brain, Akli et al. teach infection by recombination-deficient, recombinant adenovirus of brain neurons is highly localized to the area of injection (para. bridging pages 224-225). Ricordi et al. teach that gene therapy of central nervous system disorders are difficult in application because most disorders are probably multifactorial and multigenic and the target cells are located in sites that are not easily accessible. The specification does not teach what area of the brain the claimed products would need to be administered to for treatment of diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, ALS, cranial traumas and cerebral ischaemia, and the blood brain barrier would be problematic for any type of systemic administration to the brain.

Gene therapy was, at the time the invention was made, and still is, an undeveloped and highly unpredictable therapeutic modality, despite a high level of skill in the art. Orkin et al. reviews the infant state of the art of gene therapy from before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor

gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (Orkin et al., pages 1-2). Orkin et al. discloses that pre-clinical trials of adenoviral vectors revealed that the magnitude of the host response to adenoviral vectors was underestimated (page 14, 3rd bullet). Verma et al. (1997) reiterate the finding that not a single successful gene therapy protocol has been described in the art (Verma et al., page 239, para. 2), and reinforces the considerable problem posed by the immune system to any effective treatment using adenoviral vectors (Verma et al., page 241, col. 1-2). Marshall also discloses the considerable barrier to adenoviral-based gene therapy imposed by the immune system has been and continues to be a fundamental problem. This problem limits the dose range that can be employed, in that if the dose is low, the treatment is inefficient and if the dose is high the vector causes acute inflammation (Marshall, page 1052, col. 2 of box at bottom of page). Crystal also discusses the immunological barrier to adenoviral-based therapy, and also states that adenoviral vectors had been used only in human *in vivo* trials (Crystal, para. bridging pages 404-405), i.e. the prior art is silent on the use of adenoviral gene therapy vectors in any non-human animal.

Therefore, in light of the extremely limited guidance provided by the specification, the lack of working examples, the highly undeveloped and unpredictable state of gene therapy at the time the invention was made, and the problems associated with adenoviral-based gene therapy specifically and lack of experience in treatment of non-human animals with adenoviral vectors, it

would clearly require undue experimentation for the skilled artisan to use the claimed invention for the only use disclosed in the specification, *i.e.* gene therapy.

Claims 36-38 remain rejected under 35 U.S.C. 112, second paragraph, for the reasons of record set forth in the Office action of Jan. 21, 1998 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 103

Claims 27, 28, 30, 31, 34-38, 41, and 48-50 remain rejected under 35 U.S.C. 102(b)/103(a) as being unpatentable over Kahn et al. in view of Mullenbach et al. (UCLA Symp. Mol. Cell. Biol., New Ser., v. 82, pp. 313-326 (1988) for the reasons of record set forth in the Office action of January 1, 1998.

Claims 27, 28, 30, 31, 34-36, 39-41 and 48-50 remain rejected under 35 U.S.C. 102(e)/103(a) as being unpatentable over McClelland et al., U.S. 5, 543,328 in view of Mullenbach et al. UCLA Symp. Mol. Cell. Biol., New Ser., v. 82, pp. 313-326 (1988) for the reasons of record set forth in the Office action of January 1, 1998.

Claims 36-38 and 50 remain rejected under 35 U.S.C. 102(e)/103(a) as being unpatentable over McClelland et al., U.S. 5, 543,328 and Mullenbach et al. (UCLA Symp. Mol. Cell. Biol., New Ser., v. 82, pp. 313-326 (1988)) as applied to claims 27, 28, 30, 31, 34-36, 39-41, and 48-

50 above, and further in view of Akli et al. (1993) Nat. Genet. **3**: 224-228 for the reasons of record set forth in the Office action of January 1, 1998.

Conclusion

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, Ph.D., can be reached on (703) 308-2801.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

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